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1 The Safety of COVID-19 Vaccinations – Should we 2 Rethink the Policy?

3 Harald Walach ^{1*}, Rainer J. Klement ² and Wouter Aukema ³

4 1 Change Health Science Institute, Berlin, Germany

5 2 Department of Radiation Oncology, Leopoldina Hospital, Schweinfurt, Germany;

6 ORCID ID: 0000-0003-1401-4270; Email: rainer_klement@gmx.de

7 3 Independent Data and Pattern Scientist, Brinkenbergweg 1, 7351BD, Hoenderloo,

8 The Netherlands; ORCID ID: 0000-0001-7650-0093; Email:

9 wouter.aukema@gmail.com

10 * Correspondence: hwalac@gmail.com; Tel.: +49 30 467 97 436

11

12 **Abstract**

13 **Background:** COVID-19 vaccines have had expedited reviews without sufficient
14 safety data. We wanted to compare risks and benefits.

15 **Methods:** We calculated the Number Needed to Vaccinate (NNTV) from a large
16 Israeli field study to prevent one death. We accessed the Adverse Drug Reactions
17 database of the Dutch National Register (Lareb) to extract the number of cases
18 reporting severe side effects and the number of cases reporting fatal side effects.

19 **Results:** The NNTV is between 200-700 to prevent one case of COVID-19 for the
20 mRNA vaccine marketed by Pfizer. NNTV to prevent one death is between 9,000 and
21 100,000 (95% confidence interval), with 16,000 as a point estimate. We observed
22 strong variability in the number of Individual Case Safety Reports (ICSRs) per
23 100,000 vaccines doses across all EU member states. The estimate for the number of
24 ICSRs per 100,000 vaccinations derived from the Lareb database was approximately
25 700. Among those, there were 16 serious ICSRs, and the number of ICSRs reporting
26 fatal side effects was at 4.11/100,000 vaccinations. Thus, for 6 (95% CI 2-11) deaths
27 prevented by vaccination, there were approximately 4 deaths reported to Dutch
28 Lareb that occurred after vaccination, yielding a potential risk/benefit ratio of 2:3.

29 **Conclusion:** Although causality between ICSRs and vaccination has not been
30 established, these data indicate a lack of clear benefit which should cause
31 governments to rethink their vaccination policy.

32 **Keywords:** SARS-CoV2; COVID-19; vaccination; mRNA-vaccine; Number Needed to
33 Vaccinate; safety; side effects; adverse drug reaction; fatal side effects, EMA
34

36 **1. Introduction**

37 In the course of the SARS-CoV-2 pandemic, new regulatory frameworks were
38 put into place that allowed for expedited review of data and admission of new
39 vaccines without adequate and sufficient safety data. (1-3) The European Medicines
40 Agency Website
41 ([https://www.ema.europa.eu/en/human-regulatory/overview/public-health-thre](https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines;)
42 [at/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines;](https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/treatments-vaccines/covid-19-vaccines;)
43 accessed July 22nd 2021) lists all four Covid-19 vaccines that have market
44 authorization in the EU (Comirnaty [BioNTech-Pfizer], Spikevax [Moderna],
45 Vaxzevria [AstraZeneca], Covid-19 vaccine Janssen [Johnson&Johnson]) as having
46 received conditional market approval, awaiting the outcome of long-term trials. The
47 same is true for the US (see, for instance the Emergency Use Authorization for the
48 Pfizer-BioNTech vaccine (4)).

49 Many of the new vaccines use completely new technologies that have never been
50 used in humans on a large scale outside of trials so far(5). The rationale for this
51 action was that the pandemic was such a ubiquitous and dangerous threat and that
52 there was no efficacious treatment for it that this exceptional situation warrants
53 exceptional measures. Thus, the vaccination campaign against SARS-CoV-2 has
54 started beginning in January 2021 after Comirnaty was the first substance to receive
55 conditional market authorization on December 21st, 2020, followed by Spikevax
56 (Moderna) on 21st January 2021, and Vaxzevria on February 18th 2021
57 (<https://www.ema.europa.eu/en/medicines/human/EPAR/comirnaty>, accessed
58 July 22nd 2021). To date (July 22nd, 2021), roughly 435.3 million doses have been
59 administered in the EU
60 ([https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-](https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab)
61 [tracker.html#distribution-tab](https://qap.ecdc.europa.eu/public/extensions/COVID-19/vaccine-tracker.html#distribution-tab) accessed July, 22nd 2021), primarily the vector
62 vaccination product developed by the Oxford vaccination group and marketed by
63 AstraZeneca, Vaxzevria (6) (about 25% coverage in the EU), the RNA vaccination
64 product of BioNTec marketed by Pfizer, Comirnaty (7, 8) (about 60%) and the
65 mRNA vaccination product developed by Moderna (9) (about 10%). Other products
66 account for only about 5% of all vaccinations. The safety of these vaccines has been
67 tested only in comparatively short and small phase 3 trials, and long-term trials are
68 ongoing and not foreseen to end before 2022 and 2023 (2). Post-marketing
69 surveillance studies are not under way, as far as we know. A search of the trial
70 register clinicaltrials.gov on July 18th, 2021, revealed some 500 phase 2 or phase 3
71 licensing trials with long term observational periods of up to two years, but no single
72 post-marketing surveillance study registered. The ongoing long-term trials are being
73 unblinded at a fast rate, thus obfuscating potential comparisons between treatment

74 and controls (2). We therefore wanted to establish a way to determine the
75 effectiveness of the vaccines and compare them with the costs in terms of side effects.

76 **2. Methods**

77 We used the large Israeli field study testing the BioNTech vaccine (10) that
78 involved approximately 1 million persons and the data reported therein to calculate
79 the Number Needed to Vaccinate (NNTV) to prevent one case of SARS-CoV-2 and to
80 prevent one death due to COVID-19. In addition, we used the most prominent trial
81 data from regulatory phase 3 trials to assess NNTV (8, 9, 11). NNTV is the reciprocal
82 of the absolute risk difference between the control group and the test group. For
83 example: an absolute risk of 0.8 in the control group and an absolute risk of 0.3 in the
84 test group would result in an absolute risk difference of 0.5; thus, the NNTV would
85 be $1/0.5 = 2$. This is the clinical effectiveness of the vaccine. Usually, vaccine efficacy
86 is used as a measure of vaccination success. This is a measure derived from a ratio of
87 effectiveness between the groups. This veils the fact that, when incidence of an
88 infection and infectivity is relatively low, a large number of people have to be
89 vaccinated to see an effect, clinically speaking. Because we were interested in the
90 clinical effects and its relationship to side-effects which might occur in all those
91 vaccinated, we used NNTV as a clinical effect size measure.

92 We checked the Adverse Drug Reaction (ADR) database of the European
93 Medicine Agency (EMA: http://www.adrreports.eu/en/search_subst.html#;
94 accessed 28th May 2021; the COVID-19 vaccines are accessible under "C" in the
95 index). Looking up the number of single cases with side-effects reported for the three
96 most widely used vaccines (Comirnaty [BioNTech/Pfizer], vector vaccination
97 product Vaxzevria, marketed by AstraZeneca, the mRNA vaccine Spikevax by
98 Moderna) by country, we discovered that the reporting of side effects varies widely
99 between European countries. (Figure 1). On European average we see 127 Individual
100 Case Safety Reports (ICSRs), i.e. cases with side effect reports per 100,000
101 vaccinations. The Dutch authorities register 701 reports per 100,000 vaccinations,
102 while Poland registers only 15 ISCRs per 100,000 vaccinations. We know that
103 reporting standards of ADR databases are generally weak (12). In order to use data
104 that are as realistic as possible, we decided to use the ADR-database according to
105 high reporting number. We deemed it unlikely that in a country such as the
106 Netherlands the ADR-reporting would produce overestimates. Rather, we assumed
107 that the reporting standards are higher. We therefore decided to use the data of the
108 Dutch national register <https://www.lareb.nl/coronameldingen>; accessed 29th May
109 2021) to gauge the number of reported severe and fatal side effects per 100,000
110 vaccinations. We compared these quantities to the NNTV to prevent one clinical case
111 and one fatality by COVID-19.

112 **3. Results**

113 Table 1 shows the data from the Israeli field study testing Comirnaty (BioNTech/
 114 Pfizer). This was based on matched pairs, using propensity score matching with a
 115 large number of baseline variables, in which both the vaccinated and unvaccinated
 116 persons were still at risk at the beginning of a specified period (10). We use the
 117 estimates from Table 1, because they are likely closer to real life and derived from the
 118 largest field study to date. But we also report the data from the phase 3 trials
 119 conducted for obtaining regulatory approval in Table 2 and use them for a sensitivity
 120 analysis.

121 Table 1 – Risk differences and Number Needed to Vaccinate (NNTV) to prevent one
 122 case, one case of symptomatic illness and one death from COVID-19; Data from
 123 Dagan et al (10), N=596,618 in each group

124

Period	Documented infection		Symptomatic illness		Death from COVID-19		NNTV (95% CI)
	Risk difference [no./1000 persons] (95% CI)	NNTV (95% CI)	Risk difference [no./1000 persons] (95% CI)	NNTV (95% CI)	Risk difference [no./1000 persons] (95% CI)	NNTV (95% CI)	
14-20 days after first dose	2.06 (1.70- 2.40)	486 (417- 589)	1.54 (1.28- 1.80)	650 (556-782)	0.03 (0.01- 0.07)	33,334 (14,286- 100,000)	
21-27 days after first dose	2.31 (1.96- 2.69)	433 (372- 511)	1.34 (1.09- 1.62)	747 (618-918)	0.06 (0.02- 0.11)	16,667 (9,091- 50,000)	
7 days after second dose to end of follow-up	8.58 (6.22- 11.18)	117 (90- 161)	4.61 (3.29- 6.53)	217 (154-304)	NA	NA	

125 Data taken from Table 2 in Dagan et al. NNTV = 1/risk difference

126

127 Table 2 – Number Needed to Vaccinate (NNTV) calculated from pivotal phase 3
 128 regulatory trials of the SARS-CoV2 mRNA vaccines of Moderna, BioNTech/Pfizer
 129 und Sputnik (the vector vaccine of Astra-Zeneca is not contained here, as the study
 130 (13) was active-controlled and not placebo-controlled)

131

Vaccine	N participants vaccine group	N participants placebo group	SARS-CoV-2- positive end of trial group	SARS-CoV-2 - positive end of trial placebo group	Absolute Difference (ARD)	Risk Number Needed to Vaccinate 1/ARR
Moderna (9) ^{\$}	15,181 (14,550*)	15,170 (14,598*)	19 (0.13%) ¹	269 (1.77%) ¹	0.0165	61
Comirnaty (BioNTech/Pfizer) (8) ^{\$}	18,860	18,846	8 (0.042%) ²	162 (0.86%) ²	0.00817	123
Sputnik V (11) ^{\$}	14,964	4,902	13 (0.087%) ^{**3}	47 (1%) ^{**3}	0.0087	115

132 *modified intention to treat-population; basis for calculation

133 ** taken from the publication because of slightly different case numbers

134 \$ Outcome is a symptomatic COVID-19 case

135 § Outcome is confirmed infection by PCR-test

136 1 after 6 weeks

137 2 after 4 weeks

138 3 after 3 weeks

139

140 It should be noted that the cumulative incidence of the infection, visible in the
 141 control group after seven days is low (Kaplan-Meier estimate <0,5%, Figure 2 in
 142 Dagan et al.) and remains below 3% after six weeks. In the other studies, incidence
 143 figures after three to six weeks in the placebo groups are similarly low between
 144 0.86% and 1.8%. The absolute infection risk reductions given by Dagan et al. translate
 145 into NNTV of 486 (95% CI 417-589) two to three weeks after the first dose, or 117
 146 (90-161) after the second dose until the end of follow-up to prevent one documented
 147 case (Table 1). Estimates of NNTV to prevent SARS-CoV-2 infection from the phase 3
 148 trials of the most widely-used vaccination products¹⁻⁴ are between 61 (Moderna) and
 149 123 (Table 2) and estimated to be 256 by Cunningham (14). However, it should also
 150 be noted that the outcome “Documented infection” in Table 1 is SARS-CoV-2-
 151 infection as defined by a positive PCR test, i.e., without considering false positive
 152 results (15). This means that the outcome “symptomatic illness” may better reflect
 153 vaccine effectiveness. If clinically symptomatic COVID-19 until the end of follow-up
 154 is used as an outcome, the NNTV is estimated as 217 (95% CI 154-304). A
 155 comparison between the most important pivotal phase-3 regulatory trials and the
 156 Israeli field study by Dagan concluded that the Dagan study gives a robust estimate
 157 of the clinical effect (16).

158 In the Israeli field study, 4,460 persons in the vaccination group became infected
 159 as determined by PCR test and clinical symptomatology during the study period.
 160 Nine persons died, translating into an infection fatality rate (IFR) of 0.2% in the

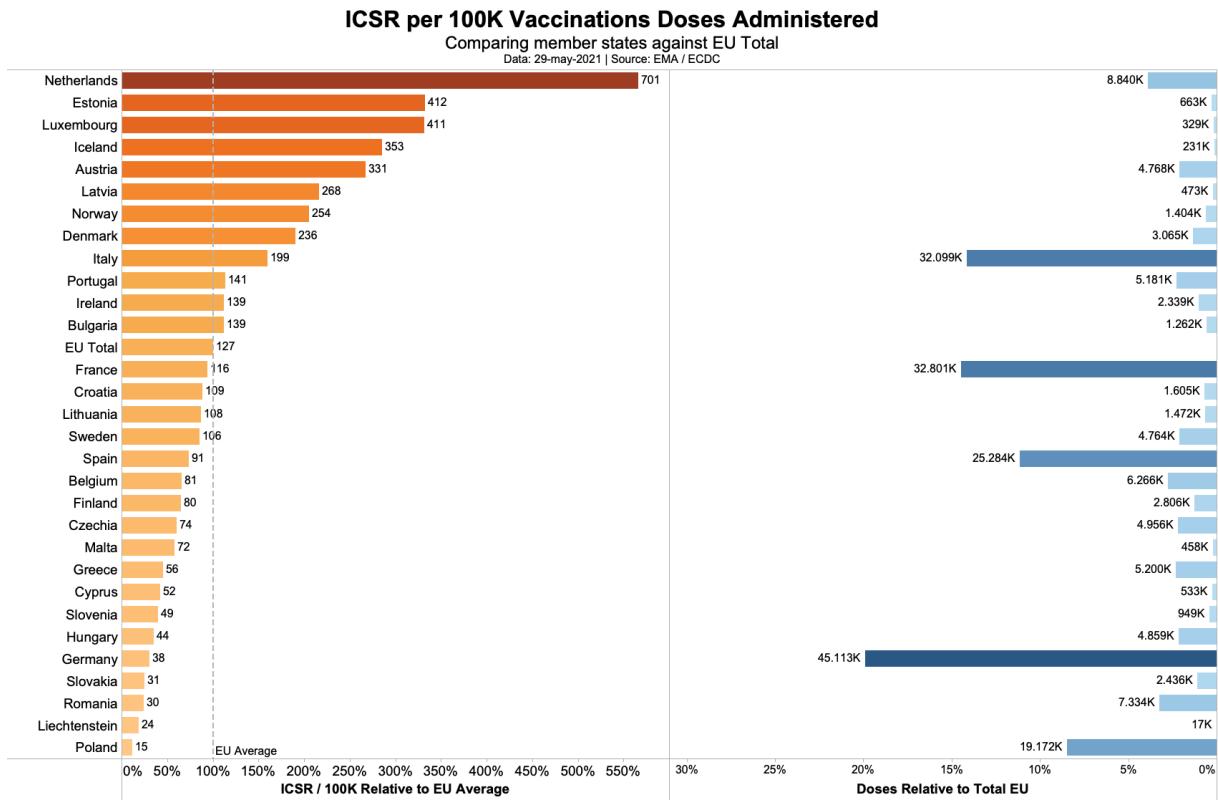
161 vaccination group. In the control group, 6,100 became infected and 32 died, resulting
162 in an IFR of 0.5%, which is within the range found by a review (17, 18).

163 Using the data from Table 1 we can calculate that the absolute risk difference is
164 0.00006 (ARD for preventing one death after 3-4 weeks), which translates to an
165 NNTV of 16,667. The 95% confidence interval spans the range from 9,000 to 50,000.
166 Thus, we need to vaccinate between 9,000 and 50,000 people, with a point-estimate of
167 roughly 16,000, to prevent one COVID-19 related death within the following 3-4
168 weeks.

169 For the other studies listed in Table 2, in the case that positive infection (i.e.
170 infection determined by a PCR test) was the outcome (11) we can calculate the
171 NNTV to prevent one death using the IFR estimate of 0.2% (18); in the case that
172 clinically positive COVID-19 was the outcome (8, 9), we can use the Case Fatality
173 Rate of 2% estimated as the number of worldwide COVID-19 cases/COVID-19
174 related deaths estimated from one of the prominent Corona dashboards
175 (<https://www.worldometers.info/coronavirus/> accessed 29th May 2021). In the case
176 of the Sputnik vaccine, one would thus have to vaccinate 5,750 to 57,500 people to
177 prevent one death. In the case of the Moderna vaccine, one would have to vaccinate
178 3,050 to 30,500 people to prevent one death. In the case of Comirnaty, the Pfizer
179 vaccine, 6,150 to 61,500 vaccinated people would prevent one death, and using the
180 figure by Cunningham (14) it would be 12,300 to 120,300 vaccinations to prevent one
181 death.

182

183 Figure 1 – Individual Safety Case Reports in Association with COVID 19 Vaccines in
 184 Europe



185
 186 The side effect data reported in the Dutch register
 187 (www.lareb.nl/coronameldingen, accessed May 27, 2021) are shown in Table 3.
 188

189

190 Table 3 – Individual Case Safety Reports for the most widely distributed COVID-19
 191 vaccines according to the Dutch side effects register
 192 (www.lareb.nl/coronameldingen), absolute numbers per vaccine and standardized
 193 per 100,000 vaccinations

194

	General Number of Reports (1)	Serious Effects Reported (1)	Side Deaths Reported(2)	Number of Vaccinations According to (3)	Number of Vaccinations according to ECDC (4)
Comirnaty(Pfizer)	21,321	864	280	5,946,031	6,004,808
Moderna	6,390	114	35	531,449	540,862
Vaxzevria (AstraZeneca)	29,865	411	31	1,837,407	1,852,996
Janssen	2,596	7	-	142,069	143,525
Unknown	129	15	5	-	540
Total	60,301	1,411	351	8,456,956	8,542,731
Per 100,000 vaccinations according to Dutch data	713.03	16.68	4.15		
Per 100,000 vaccinations according to ECDC	705.87	16.52	4.11		

195 1 <https://www.lareb.nl/coronameldingen>196 2 <https://www.lareb.nl/pages/update-van-bijwerkingen>197 3 <https://coronadashboard.rijksoverheid.nl/landelijk/vaccinaties> *198 4 ECDC: European Center for Disease Prevention and Control;
 199 <https://www.ecdc.europa.eu/en/publications-data/data-covid-19-vaccination-eu-eea>

200 All sites accessed on May 27, 2021

201 * Dutch government reports two numbers; we took the calculated amounts

202

203 Thus, there were 16 reports of severe adverse reactions and 4 reports of deaths per 100,000 COVID-19 vaccinations delivered. According to the point estimate of NNTV = 16,000 (95% CI 9,000-50,000), to prevent one COVID-19 related death, for every 6 (95% CI 2-11) deaths prevented by vaccination in the following 3 – 4 weeks there are approximately 4 deaths reported to Lareb that occurred after COVID-19 vaccination. Therefore, we would have to accept that 2 people might die to save 3 people.

211 The risk-benefit ratio looks better if the stronger effect sizes from the phase 3 trials are used for calculation. Using Cunningham's estimate of NNTV = 12,300, which stems from a non-peer reviewed comment, 8 deaths are prevented per 100,000 vaccinations and in the best case it is 33 deaths prevented by 100,000 vaccinations. Thus, in the optimum case four deaths are risked to prevent 33 deaths, a risk-benefit ratio of 1:8. The risk benefit ratio in terms of deaths prevented and possible deaths

217 associated with vaccines thus ranges from 2:3 to 1:8. It is obvious that the time period
218 of the Dagan study was much too short, as vaccinations might develop their clinical
219 effect over time, thus potentially changing the risk benefit ratio to the better.
220 Unfortunately, we do not have the data to argue this point.

221

222 4. Discussion

223

224 The COVID-19 vaccines are immunologically effective and can prevent infections,
225 morbidity and mortality associated with SARS-CoV-2 according to the data reported
226 in regulatory trials (8, 9, 13, 19). Relative risk reduction (RRR), defined as $RRR =$
227 $1 - \text{Attack Rate}_{\text{vaccinated}} / \text{Attack Rate}_{\text{unvaccinated}}$, ranges between 67% and 95% (16). In a
228 non-peer reviewed opinion blog article, Dr. Helen Petousis-Harris pointed out that
229 RRR would be the correct parameter for assessing vaccine effectiveness and criticized
230 the usage of NNTV, stating that “[v]accine effectiveness is never calculated by using
231 a

NNT/NNV

232 (<https://sciblogs.co.nz/diplomaticimmunity/2021/07/03/fundamentally-flawed-study-on-covid-19-vaccine-safety-is-rapidly-retracted/>), accessed July 30th, 2021).

233 However, as pointed out by Olliaro et al. 2021(16), “RRR considers only participants
234 who could benefit from the vaccine, [while] the absolute risk reduction (ARR),
235 which is the difference between attack rates with and without a vaccine, considers
236 the whole population”. Thus, clearly, ARR is the more robust estimate to assess the
237 clinical, not the theoretical, benefit of a vaccine (and any intervention). The ARR is
238 expressed as Number Needed to Vaccinate (NNTV), which is simply its reciprocal.
239 For the aim of our study, which was the comparison between risks and benefits in the
240 whole population, we had to use NNTV, although this measure is typically ignored
241 in vaccine effectiveness studies, because ARR “give a much less impressive effect size
242 than RRRs” (16) (Olliaro et al. 2021). Cunningham was the first to point out the high
243 NNTV in a non-peer-reviewed comment: around 256 persons to prevent one case
244 with the Pfizer vaccine (14). Olliaro and colleauges (16) remind us that NNTV
245 ranges between 78 and 119 for the regulatory trials and 217 for a naturalistic study
246 like the one by Dagan and colleagues outside a trial, thus confirming indirectly our
247 choice of our main database. This absolute effectiveness has to be compared to the
248 costs of an intervention. Apart from the economic costs, there is a comparatively high
249 rate of reported side effects, and a comparatively high rate of reported fatalities, as
250 our analysis shows. The current figure is around four fatalities reported per 100,000
251 vaccinations as documented by the Dutch side-effects register Lareb. This is in
252 agreement with a recently conducted analysis of the US Vaccine Adverse Reactions
253 Reporting System, which found 3.4 fatalities reported per 100,000 vaccinations,
254 mostly with Comirnaty (Pfizer) and Moderna vaccines.(20)

256 Is this few or many? The answer to this question is dependent on one's view of
257 how severe the pandemic is, and whether it is true that there is hardly any innate
258 immunological defense or cross-reactional immunity. Some argue that we can
259 assume cross-reactivity of antibodies to conventional coronaviruses in 30% to 81% of
260 the population (21-25). An innate immune reaction is difficult to gauge. Thus, low
261 sero-prevalence figures (18, 26, 27) may not only reflect a lack of herd immunity, but
262 also a mix of undetected cross-reactivity of antibodies or T-cell immunity to other
263 coronaviruses as well as clearing of infection by innate immunity. Thus, since natural
264 immunity is present, the necessity to induce sub-optimal immunity via vaccination
265 becomes less urgent. It might be worthwhile to study the prevalence of cross-
266 immunity mediated by T-cells more widely.

267 The study which we used to gauge the NNTV is a single field study with too
268 short an observation time, even though it is the largest to date. The other data stem
269 from regulatory trials that are not designed to detect maximum effects. The field
270 study is somewhat specific to the situation in Israel, and studies in other countries
271 and other populations, or other post-marketing surveillance studies might reveal
272 more beneficial clinical effect sizes, when the prevalence of the infection is higher.
273 Some of the cases from the field study were omitted, presumably due to a loss to
274 follow-up. However, the regulatory studies compensate for some of the weaknesses,
275 and thereby generate a somewhat more beneficial risk-benefit ratio.

276 The time frame of this study as well as that of regulatory phase 3 trials is short.
277 One could argue that this study did not provide data for death as outcome after the
278 second, but only after the first vaccination. However, if we use the outcome data after
279 the second vaccination as a proxy, which is hospitalization, there we see no
280 difference between the absolute risk difference after the first and the second
281 vaccination (data only in the original Table of Dagan et al (10)). Obvious side-effects
282 captured by ADR-reporting systems occur relatively quickly after a vaccination in
283 most cases. The analysis of the US VAERS database found that 70% of all individuals
284 reported had an onset of the ADR 48 hours after the first dose (20). As Seneff &
285 Nigh (28) show, potential late toxicities are also important but won't be captured by
286 the reporting systems. Hence, what we refer to are short term negative effects
287 reported subsequent to Covid-19 vaccinations. Supporters of such vaccinations
288 would argue that such vaccinations would only show their benefit over time. Hence,
289 ideally, a long-term study with large numbers and an observation period of 6 months
290 or longer to gauge clinical effectiveness would be needed and should have been
291 initiated. The data we used, limited as they are, are what is currently available.

292 The ADR-database of the EMA collects reports made by doctors, patients and
293 authorities. We have seen (Figure 1) that the reporting standards vary hugely across
294 countries. It might be necessary for the EMA and for national governments to install

295 better monitoring procedures in order to generate more reliable data. Some countries
296 have tight reporting schemes; some report in a rather loose fashion. As we have to
297 assume that the average number of side effects is roughly similar across countries, we
298 would expect similar reporting quota. However, upon inspection of the reports
299 according to country, we see a large variance. Our decision to use the Dutch data as
300 proxy for Europe was derived from that discovery. One might want to challenge this
301 decision. But we do not see that data from other countries are more valid in terms of
302 more diligent monitoring and confirmation than the ones we use here. Apart from
303 this, our findings correspond to previously published findings (20), which indirectly
304 provides validation of our method.

305 We emphasize that we are dealing with associations that, ideally, would have to be
306 investigated carefully for causal links using established methodologies such as the
307 Bradford-Hill Criteria (29, 30). However, the Dutch data are checked by
308 investigatorsⁱ. Thus, although direct causality cannot be inferred from these
309 databases, strong associations are possible. It is important to note: The burden of
310 proof is not on those who doubt the safety of the vaccine, but on those who proclaim
311 its safety. Our data cast doubt on that claim. Although this doubt is far from
312 incontrovertible, considering the short time frame of the data we used, it is strong
313 enough, we contend, to be taken seriously.

314 In addition, there is mechanistic evidence supporting a causal link between
315 vaccinations and reported side effects. A recent experimental study showed that the
316 SARS-CoV-2 spike protein is sufficient to produce endothelial damage (31). This
317 provides a potential causal rationale for the most serious and most frequent side
318 effects, namely vascular problems such as thrombotic events. The vector-based
319 COVID-19 vaccines can produce soluble spike proteins, which multiply the potential
320 damage sites (32). The spike protein also contains domains that may bind to
321 cholinergic receptors, thereby compromising the cholinergic anti-inflammatory
322 pathways, enhancing inflammatory processes (33). Lyons-Weiler showed that most
323 SARS-CoV-2 proteins, including the spike protein, showed more or less homology to
324 human proteins, potentially leading to immunological priming and autoimmune
325 reactions against self-antigens after vaccination (34). Finally, a recent review lists
326 several other potential side effects of COVID-19 mRNA vaccines that may also
327 emerge later than in the observation periods covered here (28).

328 In the Israeli field study, the observation period was six weeks, and in the US
329 regulatory studies, four to six weeks. Such periods are commonly assumed to be
330 sufficient to see a clinical effect of a vaccine, because it would also be the time frame
331 within which someone who was infected initially would also fall ill and perhaps die.
332 Had the observation period been longer, the clinical effect size could have increased,
333 i.e. the NNTV would have become lower and consequently the ratio of benefit to

334 harm would have increased in favor of the vaccines. However, as noted above, there
335 is also the possibility of side effects developing with some delay and influencing the
336 risk-benefit ratio in the opposite direction (28). This should be studied more
337 systematically in a long-term observational study.

338 Another point to consider is that initially mainly older persons and those at risk
339 were entered into the national vaccination programs. It is to be hoped that the tally of
340 reported fatalities associated with the vaccinations becomes lower, as the age of those
341 vaccinated decreases.

342 Given the data, we should act now and use the data available to study who
343 might be at risk of suffering side effects from COVID-19 vaccinations. Careful safety
344 monitoring needs to be put in place, together with a dedicated large scale cohort
345 study in which vaccinated individuals are followed up by medical specialists for a
346 longer period and all complaints about side effects are carefully investigated, as well
347 as all fatalities are autopsied to verify causes of side effects and deaths.

348 Finally, we note that experience with side effects reporting from other drugs has
349 shown that only a small fraction of side effects are reported to adverse events
350 databases (35, 36). The median underreporting can be as high as 95% (12).

351 **5. Conclusion**

352

353 The present assessment raises the question whether it would be necessary to rethink
354 vaccination policies. In particular, given the high number of serious side effects
355 already reported, the current political trend to vaccinate children who are at very low
356 risk of suffering from COVID-19 in the first place must be reconsidered. It is also vital
357 that these products be made accessible only to those who are willing to use them and
358 to accept potential risks that come with the products. In our view the EMA and
359 national authorities should begin a review into the safety database of COVID-19
360 vaccines, and governments should carefully re-consider their policies in the light of
361 these data. Ideally, independent scientists should be permitted to carry out thorough
362 case reviews of the very severe cases, so that there can be evidence-based
363 recommendations on who is likely to benefit from a SARS-CoV-2 vaccination and
364 who is in danger of suffering from side effects. In addition, in light of the fact that
365 SAR-CoV-2 is a BSL2 pathogen, autopsies should be carried out on every body.
366 Currently, our estimates show that we have to accept four reports of fatal and 16
367 reports of serious side effect per 100,000 vaccinations in order to save the lives of
368 eight to 33 people. This ratio might improve as more time after vaccination passes,
369 but this needs to be studied diligently.

370

371

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470 **Author Contributions:** Conceptualization, Harald Walach; Methodology, Harald
471 Walach; Writing – original draft, Harald Walach. HW is the guarantor of this work.

472 Rainer J Klement, PhD, Checked analysis for correctness and contributed to the
473 writing.

474 Wouter Aukema analysed COVID-19 vaccination volumes reported by ECDC and
475 the ICSR reports from EMA and produced graphs.

476 **Funding:** This research received no external funding.

477 **Institutional Review Board Statement:** This was a study on publicly available data
478 and a secondary analysis and as such not subject to an ethical review

479 **Data Availability Statement:** The documentation on how to extract the information
480 from the line listings of the ADR-database of the EMA, SQL scripts, and graphical
481 representations is available at <http://www.aukema.org/2021/04/analysis-of-icsr-reports-at-emaeuropaeu.html>.

483 **Conflicts of Interest:** The authors declare no conflict of interest.

52 ⁱ All reports received are checked for completeness and possible ambiguities. If necessary, additional
53 information is requested from the reporting party and/or the treating doctor. The report is entered
54 into the database with all the necessary information. Side effects are coded according to the
55 applicable (international) standards. Subsequently an individual assessment of the report is made.
56 The reports are forwarded to the European database (Eudravigilance) and the database of the WHO
57 Collaborating Centre for International Drug Monitoring in Uppsala. The registration holders are
58 informed about the reports concerning their product.
59 (<https://www.lareb.nl/media/eacjg2eq/beleidsplan-2015-2019.pdf>, page 13; accessed June
60 22nd, 2021) The head of pharmacovigilance of Lareb also stated that 58% of the reports in
61 the Dutch register stem from market authorization holders, i.e. from companies, which are
62 required by law to forward suspicions of product-related side-effects and fatalities
63 ([https://www.regulatoryscience.nl/editions/2021/12/prof.-dr.-eugene-van-puijenbroek-
64 on-the-nature-of-signals](https://www.regulatoryscience.nl/editions/2021/12/prof.-dr.-eugene-van-puijenbroek-on-the-nature-of-signals); accessed 29th June 2021).